

REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 85-109, the only claims pending and under examination.

Claims 1-84 have been canceled.

Claims 85-109 have been added. Support for new Claims 85 and 86 can be found in original Claim 1, and in the specification on p. 48, line 24 to p. 49, line 5, and p. 75, line 27 to p. 76, line 7. Support for new Claim 87 can be found in original Claim 3. Support for new Claim 88 can be found in original Claim 13. Support for new Claim 89 can be found in original Claim 14. Support for new Claim 90 can be found in original Claim 16. Support for new Claims 91-93 can be found in original Claim 22, and in the specification on p. 8, line 27 to p. 9, line 12. Support for new Claim 94 can be found in the specification on p. 65, lines 20-26. Support for new Claims 95-98 can be found in original Claim 58, and in the specification on p. 25, lines 5-15. Support for new Claim 99 can be found in original Claim 25. Support for new Claim 100 can be found in original Claim 28. Support for new Claim 101 can be found in the specification on p. 15, lines 2-3. Support for new Claims 102-103 can be found in the specification on p. 5, lines 14-26 and p. 49, lines 22-30. Support for new Claims 104-106 can be found in the specification on p. 50, lines 8-16. Support for new Claim 107 can be found in the specification on p. 56, lines 25-28. Support for new Claims 108-109 can be found in original Claims 26 and 27, and in the specification on p. 73, lines 19-28.

Accordingly, no new matter has been added. As no new matter has been added by way of these amendments, entry thereof by the Examiner is respectfully requested.

Withdrawn Rejections

The Applicants thank the Examiner for the withdrawal of the rejection of Claims 1, 3, 4, 14, 16, 19-22, 28, 41, 62, 76-79 under 35 U.S.C. § 102(b) as being anticipated by Gambardella et al. (Metabolism, 46, 3, March 1999, p. 291-297).

Double Patenting

Claims 1 and 21 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 17, and 33 of co-pending U.S. Application No. 11/592,097. As Claims 1 and 21 have been cancelled, this provisional rejection will be addressed to new claims 85 and 95.

The Office has alleged that the claims of the instant application and the cited claims of the co-pending application are not patentably distinct because both teach a method of treating an autonomic nervous system abnormality such as a renal associated condition comprising administering an agent such as metoprolol, a beta blocker (Final Office Action of 4/12/2010, p. 7 and p. 38).

However, the Applicants contend that the current claims are directed to treatment of a condition caused by an aging associated condition using at least one beta-blocker. This is in contrast to the cited claims in the co-pending application, which are directed to a method of treating a renal associated condition comprising *selectively administering a pharmacological agent to the kidney by intrarenal infusion*, in a manner effective to treat said subject for said renal condition. The current claims also include administering at least one beta-blocker such that the parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system is *analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject*. This is in contrast to the cited claims in the co-pending application, which are directed to *increasing* the parasympathetic activity/sympathetic activity ratio such that *the parasympathetic function is at least substantially equal to the sympathetic function* in said portion of the autonomic nervous system.

Accordingly, the Applicants contend that the cited claims of co-pending U.S. Application No. 11/592,097 fails to teach or suggest every element of the claims,

and therefore, the requirements for a nonstatutory obviousness-type double-patenting rejection have not been met. The Applicants respectfully request that the provisional nonstatutory obviousness-type double-patenting rejection over co-pending U.S. Application No. 11/592,097 be withdrawn.

Claim Rejection - 35 U.S.C. § 112

Claims 1, 3, 4, 11-28, 41, 62-84 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

In making the rejection, the Office has alleged that one of ordinary skill in the art would not be able to practice the full scope of the invention without undue experimentation for all the conditions listed (Advisory Action, p. 2).

Claims 1-84 have been cancelled, and new Claims 85-109 have been added. New Claims 85-109 are directed to the elected species wherein the aging associated condition is loss of parasympathetic function, the beta blocker is propranolol, and the non-beta blocker is an NSAID. Therefore, in view of the newly presented claims directed to the elected species, the Applicants contend that there is adequate written description in the specification to allow one skilled in the art to reasonably conclude that the inventors had possession of the claimed invention. The Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 1, 3, 4, 11-28, 41, 62-84 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled by the specification.

In making the rejection, the Office has alleged that the specification does not provide sufficient guidance for the current claims. The Office alleges that the specification does not reasonably provide enablement for treating all the disorders

listed in Claim 1, with the non-beta blocking agents listed in Claim 24 (Final Office Action of 4/12/2010, p 11).

As discussed above, Claims 1-84 have been cancelled, and new Claims 85-109 have been added. New Claims 85-109 are directed to the elected species of wherein the aging associated condition is loss of parasympathetic function, the beta blocker is propranolol, and the non-beta blocker is an NSAID. Therefore, in view of the newly presented claims, the Applicants contend that the current claims are adequately enabled by the specification. Accordingly, the Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

Claim Rejections - 35 U.S.C. § 102

Claims 1, 3, 4, 11-12, 15, 17, 21, 28, 41, 62, and 72 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Brevetti et al. (Brief communications, Nov. 1981, p 938-941). As Claims 1-84 have been cancelled, the rejections will be addressed with respect to the newly presented claims 85-109.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, (Fed. Cir. 1987).

The standard for anticipation under section 102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). Further, an anticipatory reference must be enabling, see *Akzo N.V. v. United States Int'l Trade Comm'n* 808 F.2d 1471, 1479, 1 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986), cert denied, 482 U.S. 909 (1987), so as to place one of ordinary skill in possession of the claimed invention. To anticipate a claim, a prior art reference must disclose every feature of the claimed invention,

either explicitly or inherently. *Glaxo v. Novopharm, Ltd.* 334 U.S. P.Q.2d 1565 (Fed. Cir. 1995).

An element of the rejected claims is a method of providing a subject known to suffer from an aging associated condition, and determining the state of the autonomic nervous system by measuring a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system. The method further includes evaluating the parasympathetic activity/sympathetic activity ratio to determine if modulation of the autonomic nervous system is needed, and administering an effective amount of at least one beta-blocker if modulation of the autonomic nervous system is needed to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject to treat the subject for the aging associated condition.

In making this rejection, the Office alleges that Brevetti teaches administration of a beta blocker such as propranolol in patients suffering from Shy Drager syndrome, which is an autonomic nervous system abnormality. The Office asserts that because Brevetti allegedly meets the structural limitations of the claim, Brevetti *inherently* teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject (Final Office Action, p. 21).

However, the Applicants respectfully disagree. Brevetti was cited for disclosing treatment of an imbalance between the alpha- and beta-adrenoreceptor activity of the sympathetic nervous system (p. 941), however Brevetti fails to teach *providing a subject known to suffer from an aging associated condition*. Further, nowhere does Brevetti specifically disclose the element of administering an effective amount of at least one beta-blocker to produce a parasympathetic

activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system *that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject*. The goal in Brevetti is treatment of low blood pressure. The Office has not pointed to any evidence that the method in Brevetti would result in a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

Accordingly, Brevetti fails to anticipate the current claims, because Brevetti fails to teach each and every element of the rejected claims. Consequently, the Applicants respectfully request that this rejection under 35 U.S.C. § 102(b) be withdrawn.

Claims 1, 21, 23-25, 28, 69, and 74-76 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Davies, et al. (The J of Intl Med Research, 1988, 16, 173-181). As Claims 1-84 have been cancelled, the rejections will be addressed with respect to the newly presented claims 85-109.

In making this rejection, the Office alleges that Davies teaches administration of a beta blocker such as propranolol in patients suffering from hypertension, an age-associated condition, which is also an autonomic nervous system abnormality. The Office asserts that because Davies allegedly meets the structural limitations of the claim, Davies *inherently* teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject (Final Office Action, p. 22).

However, the Applicants respectfully disagree. Davies discloses that ibuprofen does not substantially affect treatment of hypertension in patients on

beta-blockers or thiazides, however there is no discussion in Davies of the autonomic nervous system. Nowhere does Davies specifically disclose *determining the state of the autonomic nervous system by measuring a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system*, or the element of administering an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system *that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject*, nor has the Office pointed to evidence that the method in Davies would result in a ratio as in the current claims.

Accordingly, Davies fails to anticipate the current claims, because Davies fails to teach each and every element of the rejected claims. Consequently, the Applicants respectfully request that this rejection under 35 U.S.C. § 102(b) be withdrawn.

Claims 1, 16, and 18 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Bugiardini, et al. (Am J Cardiol, 1989, Feb 1, 63, 5, 286-90) as evidenced by Guilli, et al. (Cardiovascular Research, 2001, 208-216). As Claims 1-84 have been cancelled, the rejections will be addressed with respect to the newly presented claims 85-109.

In making the rejection, the Office alleges that Bugiardini teaches administration of propranolol to patients with X syndrome, which reduces the number of ischemic episodes per 24 hours (abstract). Guilli teach that patients with cardiac X syndrome exhibit reduced parasympathetic activity and normal sympathetic activity (abstract). The Office asserts that because Bugiardini as evidenced by Guilli allegedly meets the structural limitations of the claim, that Bugiardini *inherently* teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is

analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject (Final Office Action, p. 23).

However, nowhere does Bugiardini specifically disclose *providing a subject known to suffer from an aging associated condition, determining the state of the autonomic nervous system by measuring a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system*, or the element of administering an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system *that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject*, as in the current claims.

Accordingly, Bugiardini as evidenced by Guilli fails to anticipate the current claims, because Bugiardini fails to teach each and every element of the rejected claims. Consequently, the Applicants respectfully request that this rejection under 35 U.S.C. § 102(b) be withdrawn.

Claims 1 and 13 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Shimizu, et al. (J of the Amer. College of Cardiology, 39, 12, June 2002) as evidenced by Morita, et al. (Jpn Circ J 1996, Oct 60(10), 742-8). As Claims 1-84 have been cancelled, the rejections will be addressed with respect to the newly presented claims 85-109.

In making the rejection, the Office alleges that Shimizu teaches administration of propranolol to patients with LQT syndrome under normal tone or during sympathetic stimulation, and that Morita teaches that LQTs patients have autonomic nervous system abnormalities. The Office asserts that because Shimizu as evidenced by Morita allegedly meets the structural limitations of the claim, that Shimizu *inherently* teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous

system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject (Final Office Action, p. 24).

However, Shimizu fails to teach *providing a subject known to suffer from an aging associated condition, determining the state of the autonomic nervous system by measuring a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system*, or specifically disclose the element of administering an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system *that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject*. Further, the Office has not pointed to where the method in Shimizu would *necessarily* achieve a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

Accordingly, Shimizu as evidenced by Morita fails to anticipate the current claims, because Shimizu fails to teach each and every element of the rejected claims. Consequently, the Applicants respectfully request that this rejection under 35 U.S.C. § 102(b) be withdrawn.

Claim Rejections - 35 U.S.C. § 103

Claims 1, 63, 70, 71 and 73 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lampert et al. (The Am J of Cardiology, 91, 2, Jan 2003) and Gambardella et al. (Metabolism, 46, 3, March 1999, p. 291-297) in view of Ideker et al. (U.S. Patent No. 5,522,854). As Claims 1-84 have been cancelled, the rejections will be addressed with respect to the newly presented claims 85-109.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when

combined, teach or suggest all claim elements. See, e.g., *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, e.g., KSR at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing KSR. Further, the Supreme Court in KSR also stated that that “a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.” KSR at 1740; emphasis added. As such, in addition to showing that all elements of a claim were known in the prior art and that one of ordinary skill in the art had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

In making the rejection, the Office alleges that Lampert teaches that propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction. The Office asserts that although the reference does not explicitly teach that administration of beta blockers produces a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject, however that Lampert teaches administration of similar doses of propranolol as in the instant specification (Final Office Action, p. 25).

However, the Applicants contend that Lampert does not teach the element of *providing a subject known to suffer from an aging associated condition*. Further, there is no disclosure in Lampert that teaches or suggests that the treatment will *necessarily* result in a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

Lampert further does not suggest these elements, because the study was designed to “elucidate the mechanisms by which β blockers decrease mortality after acute myocardial infarction”. There is therefore no suggestion of *providing a subject known to suffer from an aging associated condition*. There is also no suggestion of producing a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

Ideker was cited for allegedly teaching measuring heart rate variability, with a decrease in heart rate variability indicating an increased risk of arrhythmia. However as neither reference teaches *providing a subject known to suffer from an aging associated condition*, or of producing a *parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject*, the combination of the references fails to teach or suggest all the elements of the current claims.

The Office further alleges that although Lampert does not teach determining a ratio of parasympathetic activity/sympathetic activity, Ideker, et al. allegedly teach that a preferred way of measuring the ratio of sympathetic to parasympathetic nerve activity is to measure heart rate variability, with a decrease in heart rate variability indicating an increased risk of arrhythmia (col. 3, lines 49-52). The Office alleges that one of ordinary skill in the art would have been motivated to determine the parasympathetic/sympathetic activity ratio in at least a portion of the ANS to use the ratio as an indicator of whether there is a decrease in heart rate variability that is associated with an increased risk of the onset of arrhythmia (Office Action of 10/7/2009, p. 29-30).

However, the Office has not articulated a sufficient reason why one of skill in the art would look to a ratio for assessing risk of *arrhythmia* as in Ideker in using the method of Lampert. Lampert is directed to using propranolol to decrease the "combined outcome of death, myocardial infarction, or congestive heart failure" after acute myocardial infarction (AMI) (p. 140, col. 1, para. 1). Ideker is directed to a method for detecting a high risk of arrhythmia and preventing arrhythmia by afferent nerve stimulation (abstract). To the extent that Ideker discloses determining the ratio of sympathetic nerve activity to parasympathetic nerve activity, it is for the purpose of detecting a high risk of *arrhythmia* (col. 1, lines 53 to 56). The Office has therefore not provided any reason why one of skill in the art would "use the ratio [of Ideker] as an indicator of whether there is a decrease in heart rate variability that is associated with an increased risk of the onset of arrhythmia" in the method of Lampert, because Lampert is directed to assessing the risk of *death, myocardial infarction, or congestive heart failure* after acute myocardial infarction, and not arrhythmia.

Furthermore, the Applicants contend that the reasoning relied upon by the Office must not come solely from the description of the Applicants' invention in their specification. If it does, the Examiner used impermissible hindsight when rejecting the claims. See *W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984); *In re Rothermel*, 276 F.2d 393, 396 (CCPA 1960)." (See BPAI decision of 1/15/2009 *Ex parte Vogel*, Ognibene, Bench, and Peaslee; Appeal 2008-5921)

The Applicants contend that the Office has not shown sufficient reason why one of ordinary skill in the art would have been led by the disclosure in Lampert (use of propranolol to improve recovery of parasympathetic tone in patients after AMI by assessing the outcomes of death, myocardial infarction, or congestive heart failure) to use the ratio as disclosed in Ideker (using a ratio for the purpose of detecting a high risk of arrhythmia).

Therefore, the Applicants maintain that the Office does not have support in Lampert's disclosure for the combination with Ideker. In fact, the reasoning relied upon by the Office for combining the two references appears to derive solely from the description of the Applicant's invention in their specification. The Office appears to be proposing a modification of the assessment of the risk of sudden death after AMI in Lampert by using the sympathetic activity/parasympathetic activity ratio for detecting a high risk of arrhythmia disclosed in Ideker. The Examiner's rationale for modifying Lampert's method with the ratio of Ideker therefore appears to be based upon impermissible hindsight.

Therefore, a prima facie case of obviousness has not been established because none of the cited references teach or suggest the elements of *providing a subject known to suffer from an aging associated condition*, or of administering a beta-blocker to produce a *parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject* in at least a portion of the autonomic nervous system. The combination therefore does not contain all the elements of the claimed invention, and does not render the claimed invention obvious. Furthermore, none of the references teach or suggest administering an effective amount of at least one beta blocker in response to a *determined sympathetic activity/parasympathetic activity ratio*. In addition, the Office has not articulated a sufficient reason why one skilled in the art would have modified the method in Lampert with the ratio in Ideker. Consequently, the Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 64-68 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gambardella et al. (Metabolism, 46, 3, March 1999, p. 291-297) as applied to Claims 1, 3, 4, 14, 16, 19-22, 28, 41, and 62 above in view of Mann et al. (US 2004/0147969). As Claims 1-84 have been cancelled, the rejections will be addressed with respect to the newly presented claims 85-109.

In making this rejection, the Office cites Gambardella for teaching the use of propranolol in elderly weight-losing cancer patients to block the effects of the sympathetic nervous system. However, Gambardella does not teach the elements of *providing* a subject known to suffer from an autonomic nervous system abnormality, or of administering a beta-blocker in an amount effective to produce a *parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human*, because Gambardella is directed to enhancement of daily caloric intake without increased energy expenditure (abstract). There is further no suggestion of these elements, because Gambardella is directed to enhancement of daily caloric intake without increased energy expenditure (abstract).

The Office acknowledges that Gambardella does not explicitly teach employing a control feedback loop, as in Claims 64-68. The Office therefore cites Mann for allegedly teaching therapeutic treatment for cardiac disease comprising sensors, and that patients can be titrated to appropriate beta-blocker dose levels based on the signals (Final Office Action, p. 27).

However as neither reference teaches *providing a subject known to suffer from an aging associated condition*, or of producing a *parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject*, the combination of the references fails to teach or suggest all the elements of the current claims.

The Office alleges that it would have been obvious to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann, because “one having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop in

expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions" and further, "it would have been obvious to one having ordinary skill in the art at the time of the invention that modulation of autonomic nervous system can be monitored and detected using sensor in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol" (Final Office Action, p. 28).

However, the Office has not articulated a sufficient reason why one of skill in the art would look to a system for treating cardiovascular disease as in Mann in using the method of Gambardella. Gambardella is directed to using propranolol to enhance daily caloric intake in elderly cancer patients, without increasing energy expenditure (abstract). Mann is directed to an apparatus for treating cardiovascular disease, using left atrial blood pressure sensors (abstract, [380]). To the extent that Mann discloses use of a control feedback loop, it is for the purpose of treating cardiovascular disease. The Office has therefore not provided any reason why one of skill in the art "would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions"" in the method of Gambardella, because Gambardella is directed to enhancement of daily caloric intake without increased energy expenditure in elderly cancer patients, and not to treatment of cardiovascular disease.

Furthermore, the Applicants contend that the reasoning relied upon by the Office must not come solely from the description of the Applicants' invention in their specification. If it does, the Examiner used impermissible hindsight when rejecting the claims. See *W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540,

1553 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984); *In re Rothermel*, 276 F.2d 393, 396 (CCPA 1960)." (See BPAI decision of 1/15/2009 *Ex parte Vogel*, Ognibene, Bench, and Peaslee; Appeal 2008-5921)

For the reasons discussed above, the Applicants contend that the Office has not shown sufficient reason why one of ordinary skill in the art would have been led by the disclosure in Gambardella to use the ratio as disclosed in Mann.

Therefore, the Applicants maintain that the Office does not have support in Gambardella's disclosure for the combination with Mann. In fact, the reasoning relied upon by the Office for combining the two references appears to derive solely from the description of the Applicant's invention in their specification. The Office appears to be proposing a modification of the treatment of weight losing elderly cancer patients in Gambardella by using the control feedback loop, using left atrial blood pressure sensors, for treating cardiovascular disease disclosed in Mann. The Examiner's rationale for modifying Gambardella's method with the ratio of Mann therefore appears to be based upon impermissible hindsight.

Therefore, a prima facie case of obviousness has not been established because none of the cited references teach or suggest the element of *providing a subject known to suffer from an aging associated condition*, or of administering a beta-blocker to produce *a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject* in at least a portion of the autonomic nervous system. The combination therefore does not contain all the elements of the claimed invention, and does not render the claimed invention obvious. In addition, the Office has not articulated a sufficient reason why one skilled in the art would have modified the method in Gambardella with the control feedback loop in Mann. Therefore, the combination of references does not render the current claims obvious. Consequently, the Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 80-81 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gambardella et al. (Metabolism, 46, 3, March 1999, p. 291-297) as applied to Claims 1, 3, 4, 14, 16, 19-22, 28, 41, 62, 76-79 above and in view of Walsh et al. (Support Care Cancer 2002, 10:523-528). As Claims 1-84 have been cancelled, the rejections will be addressed with respect to the newly presented claims 85-109.

In making this rejection, the Office acknowledges that Gambardella does not explicitly teach determination of parasympathetic and sympathetic activity ratio in at least a portion of the subject's autonomic nervous system, as in former Claims 80-81. The Office therefore cites Walsh for allegedly teaching methods of measuring parasympathetic and sympathetic functions of the ANS in cancer patients. The Office alleges it would have been obvious to one of ordinary skill in the art to use the method of Nelson to measure the parasympathetic and sympathetic activities to evaluate symptoms associated with ANS abnormalities (Final Office Action, p. 29).

However, the Examiner has failed to show where Walsh teaches determination of the parasympathetic and sympathetic activity *ratio*, or where Walsh teaches *administering an effective amount of at least one beta-blocker to a subject in response to said determined parasympathetic activity/sympathetic activity ratio*, as in the rejected claims.

Further, neither reference teaches the element of administering a beta-blocker in an amount effective to produce *a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human*. Neither reference suggests this element, because Gambardella is directed to enhancement of daily caloric intake without increased energy expenditure (abstract), and Walsh is directed to documenting ANS dysfunction in advanced cancer, with no suggestion of treatment (see abstract).

Therefore, a *prima facie* case of obviousness has not been established because the cited references fail to teach or suggest the elements of determination of the parasympathetic and sympathetic activity *ratio*, or of *administering an effective amount of at least one beta-blocker to a subject in response to said determined parasympathetic activity/sympathetic activity ratio*. Further, neither reference teaches or suggests administering a beta-blocker to produce a *parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject* in at least a portion of the autonomic nervous system. Consequently, the Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 82-84 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gambardella et al. (Metabolism, 46, 3, March 1999, p. 291-297) as applied to Claims 1, 3, 4, 14, 16, 19-22, 28, 41, 62, 76-79 above and in view of Jatoi et al. (*Current Management of Cancer-Associated Anorexia and Weight Loss*, Oncology, 2001). As Claims 1-84 have been cancelled, the rejections will be addressed with respect to the newly presented claims 85-109.

In making this rejection, the Office acknowledges that Gambardella does not explicitly teach administration of an NSAID. The Office therefore cites Jatoi for allegedly teaching that NSAIDs such as ibuprofen can be used to halt the wasting process associated with cancer associated weight loss. The Office alleges it would have been obvious to one of ordinary skill in the art to have administered an NSAID in treating weight loss associated with cancer (Final Office Action, p. 30).

However, as discussed above, Gambardella fails to teach administering a beta-blocker in an amount effective to produce a *parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human*, because Gambardella is directed to

enhancement of daily caloric intake without increased energy expenditure (abstract). There is further no suggestion of this element, because Gambardella is directed to enhancement of daily caloric intake without increased energy expenditure (abstract).

Jatoi was cited by the Office for teaching that NSAIDs such as ibuprofen can be used to halt the wasting process seen with cancer associated weight loss, however as Gambardella fails to teach all the element of the claimed invention, Jatoi fails to make up for this deficiency.

Therefore, a *prima facie* case of obviousness has not been established because the cited references fail to teach or suggest administering a beta-blocker to produce *a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject* in at least a portion of the autonomic nervous system. Consequently, the Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number PALO-002.

Respectfully submitted,
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